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Review Article

The chronic fatigue syndrome

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Introduction

'..... Waging war requires ..... energy, which in the end, depletes the operator and concerns the relationship between energy and stress. When the operators are human beings, it may happen that a stage is reached such that the demands being made exceed their resources to cope ..... the symptoms of such resultant stress have been given a variety of labels – shellshock, lack of moral fibre, twitch, war neurosis, battle fatigue and now post-traumatic stress disorder .....'. This is a paraphrased account of Norman Dixon's penetrating assessment of post-Gulf War battle stress in *The Times* Saturday Review of the 26 January 1991. It would apply equally to the chronic fatigue syndrome (CFS), which also has a variety of labels including the post-viral fatigue syndrome, myalgic encephalomyelitis, Royal Free disease, fibromyalgia, epidemic neuromyaesthenia, yuppy 'flu disease, chronic Epstein–Barr virus syndrome and Iceland disease. The major clinical feature is of incapacitating fatigue, often accompanied by widespread myalgia and low-spiritedness.

Symptoms

Fatigue of at least 6 months duration is a constant feature which limits the patient's day-to-day activities.[1] It is usually made worse by activity of any kind, so it becomes self-restrictive. It may prevent the patient from going out of doors, shopping, partying, taking children to school, doing housework and, of course, pursuing a job of work. Such fatigue is an intimate mixture of mind and body, and these two aspects are often indistinguishable. Physical fatigue may be linked to myalgia, whereas mental fatigue may be associated with lack of interest in all aspects of living.

Sleep disturbance is found in the majority,[2–4] who may complain of sleeping too long, or that their sleep is interrupted and unrefreshing. Other features reported in at least half of these patients include recurrent sore throat, poor concentration, deficient short-term memory and other neuropsychological complaints, headaches, tender lymph nodes, arthralgia, feverishness, allergies and gastrointestinal upset consistent with the irritable bowel syndrome.[2–4] In approximately 50% the onset of the syndrome is marked by an acute viral or glandular-fever-like illness.[5,6]

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Signs

There are virtually no abnormal signs, thereby providing the striking clinical feature that gross, incapacitating and distressing symptoms are out of proportion to the lack of physical signs.[1] There may be tender muscle areas but they are no more significant than in other, non-fatigued patients.[7] The lack of physical signs often upsets the patient, who would naturally prefer to have his symptoms supported by evidence of a viral infection or even other organic illness. This lack of correlation of symptoms and signs is underlined and aggravates patients still further when investigations ('please do everything') are all normal; reassuringly normal to the doctor but received with less enthusiasm by the patient.

Aetiology

Is it an infection?

The onset in 50% or more is an acute illness with fever and constitutional symptoms, suggesting a viral aetiology[5,6] which has been the subject of much research and debate. There have been several conflicting reports of the possible association of this complaint with Coxsackie and other enterovirus infections.[8] A recent carefully designed study found no significant difference in serum IgM and

IgG Coxsackie B antibody levels between patients and controls.[3] However, enteroviral RNA was found in muscle biopsies from fatigued patients in two studies.[9,10] Further evidence also comes from the claim that these patients are more likely to have enterovirus-specific VP1 antigen in their blood,[11] although others have cast doubt on the validity of this observation.[12] Epstein–Barr virus (EBV) has been associated with many conditions including infectious mononucleosis worldwide, Burkitt's lymphoma in malarious areas of Africa and nasopharyngeal carcinoma, especially in South-East Asia. It is also a well-recognized cause of persistent fatigue, often following acute infectious mononucleosis, and has been held to be the commonest cause of the chronic fatigue syndrome in the United States.[13–18] Apart from the temporal relationship between acute EBV and subsequent fatigue, evidence of this infection in CFS includes the detection of replicating virus in circulating lymphocytes, raised titres of antibodies to the viral capsid antigen and early antigen, and absent antibodies against the nuclear antigen in a proportion of patients.[13,16–18] The latter findings are proposed as supporting evidence for a continuing and incomplete immune response to EBV. This view has been challenged as several other studies have found no real association.[19–21]

A large number of other infectious agents have been implicated including human herpes virus Type 6, *Toxoplasma gondii*, *Brucella* species, *Borrelia burgdorferi*, *Candida albicans* and retrovirus.[22–25] At present a causal association with any individual infection remains unproven.

Is it an immunological upset?

There is evidence of qualitative and quantitative abnormalities of both T and B lymphocytes in CFS[26] but again, results have been conflicting. Some workers have found reduced circulating CD8 + ve (T8) suppressor cell counts which also had increased markers of activation (CD38 and HLA-DR). This group claims that patients in whom circulating T8 lymphocytes were found to have an increase in at least two of the surface markers CD11b, CD38 and HLA-DR had a 90% probability of having the fatigue syndrome.[27] Others have failed to demonstrate such differences although one group found a raised circulating T8 lymphocyte count in patients with a subsequent early improvement in symptoms.[28] Reduced levels of circulating natural killer (NK) cells,[3,29] C1q complement component, CD4 (helper) and CD3 positive lymphocytes have also been described.[30] One group reports a completely normal virally stimulated immune response in CFS,[31] and others have demonstrated an increase in CD56 + ve NK subsets with low levels of antibody-dependent cytotoxic cells.[32]

Evidence of an abnormal humoral immunity in CFS includes IgG deficiencies,[29,33] especially IgG1 and IgG3, reduced *in vitro* antigen-induced B cell response,[30] raised serum autoantibodies[29] and low circulating B cell counts in a minority of patients.[3] Currently available data on the nature of any dysfunction of lymphocyte-related immunity are conflicting and remain inconclusive. It is also clear that ill-health related to other specific aetiologies is associated with a similar range of immunological changes.[34]

Cytokine abnormalities have also been proposed in this condition. McDonald *et al.* have suggested that the side effects of alpha interferon, when given for the treatment of chronic hepatitis B, are so similar to the symptoms of CFS that this condition may be due to raised interferon levels.[35] In support of this hypothesis, one group found raised serum alpha interferon levels in three of 15 CFS patients, and increased 2.5 adenylate synthetase (an interferon-induced enzyme) in five of 18 patients.[36]

Further evidence comes from a study in which the peripheral blood mononuclear cells of sufferers were stimulated by virus *in vitro* and produce more alpha interferon than matched controls.[37] A similar line of argument was followed for Interleukin 2 (IL-2) in that the side effects of pharmacological doses are similar to CFS and raised serum levels have been detected in some CFS patients.[38] Others, however, have demonstrated normal IL-2 production by peripheral blood mononuclear cells *in vitro* but increased IL-1, IL-6 and tumour necrosis factor.[39] Most of this work on cytokines has looked at small numbers of patients and found abnormalities in only a minority, suggesting the need for much more evidence.

Is it a psychiatric disorder?

Physical symptoms seen in many patients with depression, such as lethargy, fatigue and disordered sleep pattern, are also found in CFS, and has led many to conclude that CFS is merely a form of atypical depression with accentuated physical manifestations.[40–42] This is supported by the finding that a high proportion of CFS patients meet the diagnostic criteria for psychiatric illness and have a high rate of pre-morbid psychiatric problems.[43] However, any patient with a chronic incurable condition is at risk of reactive depression and the standard questionnaires used in psychiatric assessment classify the sort of symptoms seen in CFS as supportive evidence of depression.[44] Some CFS patients are helped by anti-depressants, but whether their depression is primary or secondary remains unclear.[6] One group suggests that the majority of such patients are suffering from chronic habitual hyperventilation ('Effort Syndrome'), for which sedation and rehabilitation may help.[45]

Diagnosis

From the preceding discussion it is clear that there are no consistently abnormal physical findings or laboratory tests. The diagnosis therefore relies on the exhaustive exclusion of all other conditions likely to cause similar symptoms, in the presence of a typical history which should include fatigue of at least 6 months standing. The diagnostic process has been formalized and these criteria should ideally be utilized in future research to aid uniformity of definition.[1,46]

Course

Symptoms may follow a uniform or relapsing progression.[4–6] The outlook is generally uncertain,[4–6] although in the authors' experience the majority of patients spontaneously recover in the first 2 years. The prognosis seems to be unrelated to the type of onset of the disease.[5]

Treatment

A report from Sydney[33] claims that intravenous immunoglobulin was effective in a significant number of Australians, men and women in equal numbers, who had suffered for a mean of 47 months. A dose of 2 g/kg was infused over 24 hours once a month for 3 months. At the end, 43% of the immunoglobulin recipients and only 12% of those receiving maltose as control placebo had responded with a substantial reduction in symptoms and concomitant improvement in work, leisure and social activities. In precisely the same month a study from Minnesota reported no significant improvement with smaller doses (1 g/kg) over a longer period (6 months).[47] Moreover, in the latter study, major adverse reactions were observed in both treatment and placebo groups.[47] Such a clash of views needs vigorous umpiring and this was well done in a balanced editorial.[48] In terms of Davis cup tennis it was judged that both sides had achieved a commendable tie-break situation.[48] Straus, in summing up the differences between the studies, suggests that there is a residual possibility that immunoglobulin therapy may be effective.[48]

Magnesium deficiency has been postulated as a cause of the fatigue and parenteral magnesium was considered to be beneficial in such patients,[49] but Spanish workers found no differences in magnesium levels in serum, whole blood or red cells between patients or controls.[50] There have been no further reports supporting the use of magnesium, and this therapy has not been successful in the experience of the authors (unpublished observation). Other therapy reported to be of benefit includes cognitive behaviour therapy,[51] high-dose essential fatty acids (Efamol Marine)[52] and treatment for hyperventilation.[45] Meditation and other relaxation techniques also have their advocates.[53] Neither nystatin nor acyclovir seem to be of value.[23,54]

Non-specific therapy may include non-steroidal anti-inflammatory drugs for the persisting myalgia, and antidepressants for associated depression. It may be explained to patients who find the use of the latter drugs insulting, that this family of agents can be useful for other essentially 'organic' diseases such as protryptiline in the dyspnoea of emphysema and sleep apnoea, amitryptiline for postherpetic neuralgia, and imipramine in nocturnal enuresis. Many patients have benefitted and a 3 month trial may be tried. Graded exercise along the lines that proved so successful for poliomyelitis can be helpful after any initial acute phase, when rest is called for. Hydrotherapy, swimming, convalescance at a reputable spa, or intelligent physiotherapy may all be tried.

Patients are not helped by doctors who refuse to recognize the syndrome, or, alternatively, after recognizing it, pronounce dread judgement that nothing can be done. Whatever the aetiology (or aetiologies) of the condition, many patients can make a steady improvement with appropriate advice and support.

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